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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,642	03/30/2004	Nikos Pagratis	NEX87/C2	5220

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
03/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,642	PAGRATIS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,9-11,13 and 15-17* is/are rejected.

7)☒ Claim(s) *2,6,8,12,14 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 26, 2007 has been entered.

Claim Objections

Claim 4 is objected to because of the following informalities: this claim contains redundant language, reciting that the PEG has a molecular weight of "about between 10-80K". Appropriate correction is required.

Priority

No support could be found in the specifications of patents 5,475,096, 5,270,163, 5,660,985 or 5,496,938 for nucleic acid ligands targeted to TGF-β2 or methods of using such ligands. Applicant has not pointed out where these patents provide support for the

claimed invention; therefore the priority date accorded the instant application remains June 2, 1995, the filing date of patent 5,731,424.

Claim Rejections - 35 USC § 103

Claims 1, 3-5, 7, 9-11, 13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. in view of Tullis and Shah et al. (all of record).

The claims are directed to methods of inhibiting TGFβ2, targeting a nucleic acid ligand to a site in the patient, or treating a condition mediated by TGFβ2 by administration of a nucleic acid ligand targeted to TGFβ2. In specific embodiments, the nucleic acid ligand is conjugated to PEG that may have a molecular weight of 10-80K or 20-45K. These claims encompass embodiments wherein the TGFβ2 target is in a cell *in vitro* as well as embodiments wherein the TGFβ2 target is in a cell *in vivo*.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands (see column 13) include growth factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach at column 9 that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to PEG.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility-modifying moiety that may be hydrophobic and imparts amphiphilic character

to the final product. At page 7 solubility-modifying moieties are taught as including polyethylene glycol as well as lipophilic compounds such as palmitate, distearylglyceride and cholesteryl. Tullis teaches that the PEG has as many as 500 units, which would have a molecular weight within the ranges recited in the claims. Tullis teaches that the conjugates of the invention find use in drug delivery wherein the amphiphilic nature of the conjugate aids in transport across the cellular membrane.

Shah et al. teach at page 986, column 1 that TGFβ2 is one TGFβ isoform that has a role in cutaneous scarring. Shah et al. further teach on page 987 that inhibition of TGFβ2 through use of a neutralizing antibody reduced inflammatory response in healing wounds and reduced scarring.

It would have been obvious to one of ordinary skill in the art at the time of invention to make nucleic acid ligands taught by Gold et al. in order to target TGFβ2 and inhibit transforming growth factor β2. It would have been further obvious to one of ordinary skill to conjugate the ligands to a solubility modifying moiety such as PEG as taught by Tullis in order to improve cellular uptake. Gold et al. provide a motivation to use nucleic acid ligands in cells by teaching a method of isolating nucleic acid ligands to any target molecule, suggesting that growth factors are a desired target and by teaching that nucleic acid ligands can act in a fashion similar to antibodies. Shah et al. provide a motivation to target TGFβ2 by teaching its role in cutaneous scarring and that the neutralization of TGFβ2 by an antibody reduces scarring. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties such as PEG, teaching that such conjugates are readily transported across cellular membrane. One

of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to TGFβ2 because Gold et al. teach that their method is applicable to almost any target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates can be made using routine synthesis methods.

Thus, the invention of claims 1, 3-5, 7, 9-11, 13 and 15-17 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejection by arguing inhibition of TGFβ2 using a TGFβ2 nucleic acid ligand is not a predictable result in view of the cited references because use of an antibody that interferes with TGFβ2 does not predict success for a nucleic acid ligand, which binds through a different mechanism. This argument appears to be stating that because an antibody is a protein and a nucleic acid ligand is a nucleic acid, the binding occurs by a different mechanism. This argument is not persuasive because while nucleic acid ligands and proteins are not identical molecules, they each bind their target by assuming a specific three dimensional structure and associating with the target. Gold et al. explicitly teach that nucleic acid ligands have the same use as antibodies and even refer to nucleic acid ligands as nucleic acid antibodies. Gold et al. further teach that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Thus, while absolute success

cannot be predicted *a priori*, based on the known similarities between nucleic acid ligands and antibodies, there is a reasonable expectation that a TGFβ2 nucleic acid ligand will inhibit TGFβ2 in a fashion similar to that seen with TGFβ2 antibodies.

Applicants further argue the addition of PEG is not obvious in view of Tullis and Gold because Tullis teaches the use of nucleic acid conjugates in relation to intracellular events. Applicants conclude that Tullis is limited to conjugates providing increased cellular uptake and increased stability of normal nucleic acids, while the present invention teaches use of conjugates yielding higher serum stability and because TGFβ2 is an extracellular moiety the ability to cross the cellular membrane is not an issue. Applicants further note nucleic acid ligands are not normal nucleic acids and assert there is no motivation to combine the properties of Tullis to increase cellular uptake of nucleic acids where the nucleic acid ligand target is secreted.

The argument regarding nucleic acid ligands not being "normal" nucleic acids appears to be defining normal nucleic acids as those that act through hybridization and nucleic acid ligands as not normal because they do not act through hybridization. However the question of whether one is motivated to make a conjugate of a nucleic acid is not based on whether the nucleic acid acts through hybridization, but whether one wants to provide stability to the nucleic acid. Because those in the art recognize that use of nucleic acids in an organism requires protection from nucleases, there is a motivation to modify nucleic acids in ways that provide the stabilization required for *in vivo* use. Applicants' arguments regarding Tullis stating a different use for a conjugate are not persuasive because Tullis teaches that conjugates provide stability against

nucleases, which also provides the serum stability applicants state as their intended purpose of the conjugate. The stabilization of a conjugate occurs regardless of whether the nucleic acid is intended to cross a cellular membrane and whether the nucleic acid acts through hybridization.

Applicants argue there is an absence of predictable results with regard to a TGFβ2 nucleic acid ligand that binds to and inhibits the function of TGFβ2 protein, asserting that Gold et al. cannot predict a functional nucleic acid ligand to TGFβ2 and there was nothing in the art to suggest the functionality of the TGFβ2 nucleic acid ligand. This is not persuasive because Gold et al. while Gold et al. do not specifically teach nucleic acid ligands to TGFβ2, they teach that their method of producing nucleic acid ligands is applicable to almost any target; applicants have provided no specific reason why the SELEX method taught by Gold et al. would not identify nucleic acid ligands to this protein.

Applicants further argue there is not a reasonable expectation of success in combining the references, arguing that nucleic acid ligands are not equivalent to the nucleic acids described by Tullis, noting that nucleic acid ligands are characterized by exhibiting high specificity binding to a given target molecule. Applicants argue that for nucleic acid ligands, the three dimensional structure is of key importance and submit that the teachings of Gold et al. do not provide a reasonable expectation that a functional TGFβ2 nucleic acid ligand conjugate will be obtained.

The examiner acknowledges that nucleic acid ligands have certain characteristics different from those of the antisense sequences used in the Tullis

reference, however, the person of ordinary skill in the art recognizes based on the teachings of Gold et al. that the usefulness of a nucleic acid ligand rests on its affinity for a target and that in order for the claimed method to be useful the nucleic acid ligand would have to maintain its affinity.

Applicants assert the possible disruption of three dimensional structure of the nucleic acid ligand with the addition of a non-immunogenic, high molecular weight compound or lipophilic compound is a parameter that may have precluded any successful result. These arguments are not persuasive because the examiner recognizes that it is impossible to determine *a priori* whether a particular conjugate will affect target affinity of a nucleic acid ligand, but such a determination is not required to conclude there is a reasonable expectation of success in making conjugates of nucleic acid ligands that substantially maintain their binding affinity. In view of the advanced state of the art regarding conjugation of molecules to nucleic acids and the recognition by those in the art that conjugates can be produced by attachment at numerous points within a nucleic acid using routine synthetic methods, determining that a conjugate maintains its affinity is routine and predictable.

Applicants argue Tullis does not provide a finite number of identified, predictable solutions with a reasonable expectation of success to create a TGFβ2 nucleic acid ligand that will maintain its tertiary structure with a conjugate and inhibit TGFβ2. This argument is not persuasive because the rejection is based on the combination of the references, not Tullis alone, and Tullis is not relied upon to specifically provide these teachings.

Allowable Subject Matter

Claims 2, 6, 8, 12, 14 and 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Tracy Vivlemore/
Examiner
Art Unit 1635

TV
March 5, 2008